sample from an individual not having the malignancy indicates the presence of the malignancy in the patient.

91. (Twice Amended) A method of screening for the presence of a disease or disorder of the nervous system characterized by an aberrant level of a Notch protein or a molecule [having antigenicity of a Notch protein] capable of being bound by an anti-Notch antibody in a patient, comprising measuring the level of expression of a Notch protein or of a molecule capable of being bound by an anti-Notch antibody in a sample derived from the patient, in which an increase or decrease in the Notch protein or molecule in the patient sample relative to the level found in such a sample from an individual not having the disease or disorder indicates the presence of the disease or disorder in the patient.

92. (Twice Amended) A method of screening for the presence of a benign dysproliferative disorder characterized by an aberrant level of a Notch protein or a molecule [having antigenicity of a Notch protein] capable of being bound by an anti-Notch antibody in a patient, comprising measuring the level of expression of a Notch protein or of a molecule capable of being bound by an anti-Notch antibody in a sample derived from the patient, in which an increase or decrease in the Notch protein or molecule in the patient sample relative to the level found in such a sample from an individual not having the disorder indicates the presence of the disorder in the patient.

REMARKS

Applicants and Applicants' representatives thank Examiner Toni Scheiner for her courtesy during the telephonic interview of December 19, 1996 for the above-identified application.

Claims 68-74, 91, and 92 are pending.

Claims 68, 91 and 92 have been amended to more particularly point out and distinctly claim that which Applicants regard as the invention, to clarify that the screening methods of the present invention are characterized

by the level of Notch protein or "molecule capable of being bound by an anti-Notch antibody". The amendment to the claims is supported in the specification as filed at page 36, lines 15-28.

1. <u>Interview Summary Record</u>

A telephonic interview in connection with the above-identified patent application was held December 19, 1996, between Examiner Toni Scheiner and Attorneys for Applicants Adriane M. Antler and Kenley K. Hoover.

The Examiner's outstanding rejections were discussed during the interview.

During the interview, Examiner Scheiner indicated that substitution of the language "a molecule having the antigenicity of a Notch protein" with the recitation "a molecule capable of being bound by an anti-Notch antibody" would overcome the outstanding rejections of claims 68-74, 91 and 92 under 35 U.S.C. § 112, first and second paragraphs.

Attorneys for Applicants discussed the reasons that Ellisen *et al.*(1991, *Cell* <u>66</u>:649-661) ("Ellisen") did not render obvious the claimed invention; these reasons are discussed in detail *infra* in Section 3 of this Amendment.

The Examiner agreed that in view of Applicants' remarks, Ellisen does not suggest that increased or decreased expression of TAN-1 is associated with malignancy, disease, or disorder, and accordingly, that Ellisen does not render the claimed invention obvious under 35 U.S.C. § 103.

The Examiner further indicated that an amendment to the claims substituting the language "a molecule having the antigenicity of a Notch protein" with the language "a molecule capable of being bound by an anti-Notch antibody" would place the application in condition for allowance, subject to an interference search.

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2. The Examiner's Rejection Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 68-74, 91 and 92 are rejected under 35 U.S.C. § 112, first and second paragraphs for lack of enablement and/or for failing to particularly point out and distinctly claim the invention, because, according to the Examiner:

> The recitation "a molecule having the antigenicity of a Notch protein" is vague and indefinite because no particular portion of Notch is identified; the new recitation is still broad enough to encompass epidermal growth factor since both Notch and EGF contain the same cysteine-rich EGF repeats, and thus both have Notch "antigenicity." The specification is not enabling for correlating the presence of malignancies, nervous system disorders, or benign disproliferative disorders with aberrant expression of proteins with Notch "antigenicity."

Applicants have amended the claims to substitute the language "a molecule having the antigenicity of a Notch protein" with the recitation "a molecule capable of being bound by an anti-Notch antibody". During the telephonic interview held December 19, 1996, Examiner Scheiner informed Attorneys for Applicants, that this language substitution would overcome the outstanding rejections of claims 68-74, 91 and 92 under 35 U.S.C. § 112, first and second paragraphs. Accordingly, Applicants submit that the amendment to the claims has obviated the rejection of the claims under 35 U.S.C. § 112, first and second paragraph, and respectfully request withdrawal of the rejection.

Nevertheless, Applicants also respectfully disagree with the bases for the Examiner's rejection. Applicants point out that each EGF-like repeat of Notch is so named because of a conserved arrangement of 6 cysteines within a sequence of approximately 40 amino acids. The amino acid sequence between these conserved cysteines differ both among Notch EGF-like repeats, and between Notch EGF-like repeats and the EGF repeats of epidermal growth factor (see Ellisen et al., Fig. 4A). There is no evidence that antibodies to EGF repeats of epidermal growth factor cross-react with Notch EGF-like

repeats. Applicants further submit that even if assuming *arguendo*, such cross-reactivity exists, appropriate controls may routinely be applied to account for the cross-reactivity, as there is no evidence that cross-reactivity would detrimentally affect the ability to carry out the claimed method, or routine methods may be used to select antibodies that do not exhibit such cross-reactivity.

3. <u>The Rejection Under 35 U.S.C. § 103</u>

Claims 68-74, 91 and 92 remain rejected under 35 U.S.C. § 103 as being obvious over Ellisen et al. The Examiner contends that:

> Ellisen *et al*. disclose the human Notch homolog TAN-1 and suggest that alterations in the structure and expression of TAN-1 contribute to transformation or progression in some T-cell neoplasms, and to neural differentiation. Ellisen *et al*. do not screen for malignancy, diseases or disorders of the nervous system, or benign disproliferative disorder using TAN-1 levels, but it would have been obvious for one of ordinary skill in the art to have done so because Ellisen *et al*. suggest that there is a correlation between aberrant TAN-1 expression and malignancy, diseases or disorders of the nervous system, and benign disproliferative disorder.... Ellisen *et al*. show that aberrant expression is associated with malignancy or nervous system disorders....

Applicants respectfully disagree with the Examiner's rejection. Ellisen et al. does <u>not</u> teach that aberrant expression of a Notch protein (or of a protein capable of being bound by anti-Notch antibody) is associated with malignancy or nervous system disorders or benign dysproliferative disorders. Ellisen et al. does <u>not</u> render any conclusions regarding levels of Notch protein expression in normal versus diseased tissue. With regard to <u>gene</u> expression, Ellisen et al. teaches that TAN-1 is relatively overexpressed in lymphoid tissues (i.e., tissue of the thymus, spleen and/or lymph nodes) relative to other tissues (p. 649, col. 2), and that the 5' half of TAN-1 was transcribed at higher levels than the 3' half of TAN-1 in SUP-T1 cells (p.

655, col. 2, and Fig. 8B). There is no teaching of aberrant protein levels. As remarked by attorneys for Applicants during the telephonic interview of December 19, 1996, Ellisen does not teach or suggest the diagnostic methods of the present invention of screening for the presence of a malignancy, disease or disorder of the nervous system, or benign dysproliferative disorder, characterized by an increased or decreased level of Notch protein or molecule capable of being bound by an anti-Notch antibody in a patient. In support of this assertion, Applicants reiterate, as set forth in the Amendment filed April 4, 1996 (pages 9-12), that Ellisen cannot render the claimed invention obvious because the effect of a translocation within a gene upon the expression of the product of that gene is unpredictable, i.e., the presence of truncated *TAN-1* RNA transcripts do not indicate whether the expression of encoded *TAN-1* protein or, in particular, molecules capable of being bound by an anti-Notch antibody, is increased, decreased or remains the same, much less in a manner so as to provide diagnostic utility. In further support of this assertion, Applicants direct the Examiner's attention to the statement in Ellisen (page 658, col. 2) that "[t]he mechanism by which recombination within the *TAN-1* gene exerts its presumed effect in ALL [lymphoblastic leukemia] is at present not clear" and to the fact that the authors of Ellisen are limited to speculating as to possible hypothetical mechanisms by which the *TAN-1* translocation exerts an effect in lymphoblastic leukemia (see pages 658-659 in which, for example, the authors speculate that TAN-1 is a tumor suppressor gene, or that the TAN-1 product has lost its extracellular domain).

In the telephone interview of December 19, 1996, upon reconsidering Applicants' argument, the Examiner agreed that Ellisen does not teach a correlation between increased or decreased expression of a Notch protein, or molecule capable of being bound by an anti-Notch antibody, and the presence of a malignancy, disease or disorder.

A *prima facie* case of obviousness is established only when the teachings from the prior art itself would appear to

have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 26 U.S.P.Q.2d, 1529, 1531 (Fed. Cir. 1993). The art must suggest how to apply its teachings to the specifically claimed invention.

The Ellisen reference does not suggest the described and claimed screening methods of the present invention. Accordingly, a *prima facie* case of obviousness has not been established and in light of the arguments presented above, the rejection under 35 U.S.C. § 103 should be withdrawn. The same is believed proper, and is respectfully requested.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. In view of the above amendments and comments, it is believed that the Examiner's rejections under 35 U.S.C. § 112, first and second paragraphs, and 35 U.S.C. § 103 have been overcome and that the present application is in condition for immediate allowance. Withdrawal of the Examiner's rejections and early notice to this effect is earnestly solicited. If any issues remain, the Examiner is respectfully requested to telephone Adriane M. Antler to discuss the same.

Respectfully submitted,

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